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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/715,823	11/19/2003	Pnina Fishman	FISHMAN11A	3649

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EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 12/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/715,823	FISHMAN, PNINA	
	Examiner	Art Unit	
	Patrick T. Lewis	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-14 and 28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-14 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's Response Dated October 28, 2005

1. Claims 1, 5-14 and 28 are pending. An action on the merits of claims 1, 5-14 and 28 is contained herein below.

2. The rejection of claims 15-27 under 35 U.S.C. 101 has been rendered moot in view of applicant's amendment dated October 28, 2005.

3. The rejection of claims 1-3, 15-16 and 28 under 35 U.S.C. 112, second paragraph, has been rendered moot in view of applicant's amendment dated October 28, 2005.

4. The rejection of claims 15-27 under 35 U.S.C. 112, second paragraph, has been rendered moot in view of applicant's amendment dated October 28, 2005.

5. The rejection of claims 1-27 under 35 U.S.C. 102(b) has been rendered moot in view of applicant's amendment dated October 28, 2005.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claim 28 is rejected under 35 U.S.C. 102(b) as anticipated by Baharav et al. International Journal of Molecular Medicine, (2002) Vol. 10, No. Supplement 1, pp.

S104, Meeting info: 7th World Congress on Advances in Oncology and the 5th International Symposium on Molecular Medicine, Hersonissos, Crete, Greece, October 10-12, 2002 (Baharev).

Baharev teaches the effect of adenosine and the A3 adenosine receptor agonist IB-MECA on joint inflammation and autoimmune disease models. A3 adenosine receptor (A3AR) activation inhibits the production of anti-inflammatory cytokines such as tumor necrosis factor-alpha (TNF), interleukin 12 and interferon-gamma. The aim of the study was to explore the effect of adenosine and its A3AR agonist, IB-MECA on the development of inflammatory reaction in different models of arthritis. Three experimental animal models were used: **a**) zymosan induced arthritis (ZIA) – adenosine (0, 0.25 and 0.5 mg/kg) was introduced intraperitoneally every second day; **b**) adjuvant arthritis (AA) – IB-MECA (10 or 100 μg/kg) was introduced orally every day, started seven days after immunization; **c**) a newly developed model for Behqet disease induced by tropomyosin, manifested by arthritis (TIA) – treatment as in **b**. Arthritis intensity was evaluated clinically by knee swelling measurements and by histology. In the AA and TIA models a dose dependent anti-inflammatory effect was noted. Some of the treated animals did not develop clinical arthritis at all and the remainder animals had significantly milder synovitis.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1, 5 and 8-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baharav et al. International Journal of Molecular Medicine, (2002) Vol. 10, No. Supplement 1, pp. S104, Meeting info: 7th World Congress on Advances in Oncology and the 5th International Symposium on Molecular Medicine, Hersonissos, Crete, Greece, October 10-12, 2002 (Baharev) in combination with Burkly et al. US 6,323,027 (Burkly).

Claims 1, 5 and 8-14 are drawn to a method for the treatment of inflammatory arthritis in a human subject comprising orally administering to an individual in need of such treatment an effective amount of an active agent consisting essentially of IB-MECA or Cl-IB-MECA.

Baharev teaches the effect of adenosine and the A3 adenosine receptor agonist IB-MECA on joint inflammation and autoimmune disease models. A3 adenosine receptor (A3AR) activation inhibits the production of anti-inflammatory cytokines such as tumor necrosis factor-alpha (TNF), interleukin 12 and interferon-gamma. The aim of the study was to explore the effect of adenosine and its A3AR agonist, IB-MECA on the development of inflammatory reaction in different models of arthritis. Three experimental animal models were used: **a**) zymosan induced arthritis (ZIA) – adenosine (0, 0.25 and 0.5 mg/kg) was introduced intraperitoneally every second day; **b**) adjuvant arthritis (AA) – IB-MECA (10 or 100 μg/kg) was introduced orally every day, started seven days after immunization; **c**) a newly developed model for Behqet disease induced

by tropomyosin, manifested by arthritis (TIA) – treatment as in **b**. Arthritis intensity was evaluated clinically by knee swelling measurements and by histology. In the AA and TIA models a dose dependent anti-inflammatory effect was noted. Some of the treated animals did not develop clinical arthritis at all and the remainder animals had significantly milder synovitis.

Baharev differs from the instant method in that Baharev does not explicitly teach the treatment of humans (uses animal model); however, this deficiency would have been obvious in view of the teachings of Burkly.

Burkly teaches that animal models of rheumatoid arthritis have been established and characterized in a variety of species, including mice, rats and non-human primates (column 31, line 51 to column 32, line 28). Experimental models of arthritis with clinical and histopathological features similar to those in humans can be induced by a variety of agents.

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat a human having inflammatory arthritis using the method and amounts taught by Baharev. The use of animal models for accessing the therapeutic effects of an active agent for treating inflammatory arthritis was well known in the art at the time of the instant invention. In the absence of some unexpected result, the instant method is prima facie obvious.

10. Claims 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baharav et al. International Journal of Molecular Medicine, (2002) Vol. 10, No. Supplement 1, pp. S104, Meeting info: 7th World Congress on Advances in Oncology

and the 5th International Symposium on Molecular Medicine, Hersonissos, Crete, Greece, October 10-12, 2002 (Baharev) in combination with Burkly et al. US 6,323,027 (Burkly) as applied to claims 1, 5 and 8-14 above, and further in view of Jacobsen et al. US 5,773,423 (Jacobsen).

Claims 6-7 are drawn to a method wherein the active agent is administered twice a day.

Neither Baharev nor Burkly explicitly teach administering IB-MECA twice daily; however, this deficiency would have been obvious in view of Jacobsen.

Jacobsen teaches compounds which have been found to be selective A_3 adenosine receptor agonists, pharmaceutical compositions containing such compounds, and related treatment methods and assay methods (column 2, line 59 to column 3, line 33). The modification of adenosine at the 5'-position and/or at the N^6-position with groups that enhance A_3 potency has been found to result in moderate A_3 selectivity. In particular, the 5'-methyluronamide modification of adenosine and the N^6-benzyl group, either alone or in combination, increases affinity in binding to A_3 receptors relative to A_1 and A_{2a} receptors. Optimization of substituent groups has led to the development of the highly potent A_3 agonist N^6-(3-iodobenzyl)-adenosine-5'-N-methyluroamide (IB-MECA) which is 50-fold selective for A_3 vs. either A_1 or A_2 receptors. Triple substitution of adenosine results in the further enhancement of the degree of A_3 selectivity. 2-Chloro-N^6-(3-iodobenzyl)-adenosine-5'-N-methyluronamide (Cl-IB-MECA) has been found to be the most potent and selective agent in binding assays and has been shown to be a full agonist in the inhibition of adenylate cyclase. Disease states and conditions that may

be chronically treated include inflammatory disorders such as vascular inflammation and arthritis, Parkinson's disease, and cardiac disease (column 25, line 20 to column 26, line 19). One skilled in the art will recognize that dosage will depend upon a variety of factors including the strength of the particular compound employed, the age, species, condition, and body weight of the animal, as well as the severity/stage of the disease or condition (column 26, line 61 to column 27, line 23). The size of the dose will also be determined by the route, timing, and frequency of administration as well as the existence, nature, and extent of any adverse side effects that might accompany the administration of a particular compound and desired physiological effect. It will be appreciated by one of skill in the art that various conditions or disease states, in particular chronic conditions or disease states, may require prolonged treatment involving multiple administrations. Suitable doses and dosage regimens can be determined by conventional range-finding techniques known to shoes of ordinary skill in the art. Therapeutically effective dosages range from about 0.01 to about 10 mg/kg body weight/day. There are a wide variety of suitable formulations including formulations for oral, aerosol, parenteral, subcutaneous, intravenous, intramuscular, interperitoneal, rectal, and vaginal administration (column 19, lines 59-67).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer IB-MECA to the patient twice daily. Jacobsen teaches that one skilled in the art will recognize that dosage will depend upon a variety of factors including the strength of the particular compound employed, the age, species, condition, and body weight of the animal, as well as the severity/stage of the disease or condition

(column 26, line 61 to column 27, line 23). Suitable doses and dosage regimens can be determined by conventional range-finding techniques known to shoes of ordinary skill in the art. In the absence of some unexpected result, the instant method is prima facie obvious.

Conclusion

11. Claims 1, 5-14 and 28 are pending. Claims 1, 5-14 and 28 are rejected. No claims are allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

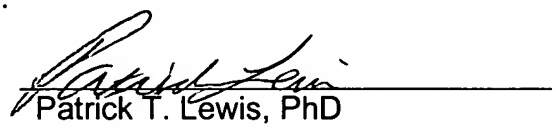
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 571-272-0655. The examiner can normally be reached on Monday - Friday 10 am to 3 pm (Maxi Flex).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Patrick T. Lewis, PhD
Primary Examiner
Art Unit 1623

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